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Early and Five-year Amputation and Survival Rate of Diabetic Patients with Critical Limb Ischemia: Data of a Cohort Study of 564 Patients

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Objective. *To evaluate the early and late major amputation and survival rates and related risk factors in diabetic patients with critical limb ischemia (CLI).*
Design. *Retrospective study.*
Methods. *Revascularization feasibility, major amputation, survival rate and related risk factors were recorded in 564 diabetic patients consecutively hospitalized for CLI from 1999 to 2003 and followed until June 2005.*
Results. *Peripheral angioplasty (PTA) was carried out in 420 (74.5%), bypass graft (BPG) in 117 (20.7%) patients. In 27 (4.8%) patients both PTA and BPG were not possible. Twenty-three above-the-ankle amputations (4.1%) were performed at 30 days: 6 in PTA patients, 3 in BPG patients, 14 in non revascularized patients. In the follow-up of 558 patients (98.9%), 62 repeated PTAs and 9 new BPGs, 32 new major amputations (16 in PTA patients, 14 in BPG patients and 2 in non-revascularized patients) were performed. Major amputation was associated with absence of revascularization (OR 35.9, $p < 0.001$, CI 12.9–99.7), occlusion of each of the three crural arteries (OR 8.20, $p = 0.022$, CI 1.35–49.6), wound infection (OR 2.1, $p = 0.004$ CI 1.3–3.6), dialysis (OR 4.7, $p = 0.001$ CI 1.9–11.7) increase in $TcPO_2$ after revascularization (OR 0.80, $p < 0.001$ CI 0.74–0.87).*

One hundred seventy three patients died during follow-up and this was associated with age (HR 1.05, $p < 0.001$ CI 1.03–1.07), history of cardiac disease (HR 2.16, $p < 0.001$ CI 1.53–3.06), dialysis (HR 3.52, $p < 0.001$ CI 2.08–5.97), absence of revascularization (HR 1.68, $p < 0.001$, CI 1.29–2.19) and impaired ejection fraction (HR 1.08, $p < 0.001$, CI 1.05–1.09).
Conclusions. *In diabetic patients with CLI the revascularization is feasible in most cases and allows a low rate of early major amputation. This rate is higher in the follow-up period. Major amputation is very high in patients where revascularization is not feasible while the high mortality rate is due to the serious comorbidities observed in these patients.*

Keywords: Diabetic foot; Critical limb ischemia; Peripheral angioplasty; Peripheral bypass graft; Above-the-ankle amputation; Survival.

Studies on diabetic patients with peripheral arterial disease support the effectiveness of revascularization,[1–3] however very few studies report the outcomes of patients unsuitable for revascularization.[4] We do not know any study in diabetic population that used the diagnostic criteria of critical limb ischemia (CLI) proposed in 2000 by TransAtlantic Inter-Society Consensus (TASC).[5]

The purpose of this study is to evaluate the outcomes of diabetic patients with TASC criteria of CLI. We report the feasibility of revascularization with peripheral angioplasty (PTA) or bypass graft (BPG), the early major amputation rate, the incidence of redo vascular procedures and of new major amputations, the survival rate and related risk factors for amputation and survival in diabetic patients consecutively hospitalized for CLI.

Materials and Methods

Protocol

All diabetic patients referred to our Diabetic Foot Centre were assessed for the presence of sensory-motor neuropathy and peripheral arterial occlusive disease.

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Sensory-motor neuropathy was detected by means of vibration perception threshold > 25 V at biothesiometer, insensitivity in >5/9 foot points at Semmes-Weinstein 10 g filament, and absence of Achilles' tendon reflex. Peripheral arterial disease was suspected if one foot pulse was reduced or absent, ankle-pressure was <70 mmHg when assessable, transcutaneous oxygen tension ($TcPO_2$) at the dorsum of the foot was <50 mmHg, and significant obstructions were present at duplex scanning. All patients with these parameters were referred to an angiographic study and, if obstruction > 50% of vessel diameter was present, PTA was performed in the same session.[6] In patients unsuitable for PTA a by-pass graft (BPG) was considered. The patients in whom PTA or BPG were not possible, received a therapy with prostanoids (alprostadil-α-ciclodextrine 60−120 μgr/day) and percutaneous sympathectomy with phenol injection under CT guidance.

In patients in whom therapies did not relieve the rest pain or the gangrene was extended above the Chopart joint, major amputation was performed.

For all patients, antalgic medication, $TcPO_2$ and ankle pressure were reassessed 5 days after the PTA, BPG, sympathectomy or prostanoids infusion.

Limb salvage

In patients complaining of rest pain without foot ulcer, the disappearance of pain with discontinuation of antalgic therapy was considered to be a successful limb salvage. In patients with foot ulcer we considered limb salvage successful when the ulcer healed and plantar stand was maintained, even when achieved by tarsal-metatarsal amputation[7,8] and the patient was able to walk without crutches or artificial leg. Conversely, any above-the-ankle amputation was considered a failure (major amputation).

Complications

Any event that required specific medical or surgical treatment or prolonged hospital stay following PTA or BPG was recorded and considered a complication. Haematoma formation at the puncture site was considered not significant unless necessitating either surgery and/or packed red blood cell transfusion.

Follow-up

After hospital discharge all patients with foot ulcer were examined weekly until ulcer healing. All patients were provided with extra-deep rocker shoes with soft thermoformable leather and customized insoles. Restenosis after PTA was suspected when pain or an ulcer recurred. In these situations ankle-pressure and $TcPO_2$ were reassessed and duplex scanning was performed.[9] If ankle pressure and $TcPO_2$ were significantly worse (<15% of the post-PTA value) and Duplex scanning was positive, the patient underwent a new angiographic evaluation and a further PTA, if possible, or a BPG, if PTA impossible, was performed. Morphological restenosis was not investigated since in absence of rest pain or ulcer reappearance we do not perform any revascularization, therefore we consider it clinically irrelevant.[10] BPGs were followed according to the vascular surgery protocol.[11] The graft patency was assessed with clinical examination and ultrasound study at 30 days, 3,6,12 months and thereafter every 6 months.

For every invasive treatment (PTA, BPG, sympathectomy, surgical operation on the foot) the written informed consent form was obtained from the patient.

PTA clinical restenoses, BPG closures, repeat vascular procedures, new above-the-ankle amputations, vital status as well as date and cause of deaths were recorded.

Statistical methods

Descriptive statistics were reported as average values and 1 standard deviation (SD) for continuous variables and as percentages for discrete variables.

The relationship among the considered variables and the risk of above-the-ankle amputation was evaluated by multiple logistic regression and data were reported with odds ratio (OR) and 95% CI. The Cox regression model was adopted and Hazard Ratio (HR) for the tested variables was reported in order to check the association of patients characteristics and the life time lasted from the entry in the study until the death or study closure. The time to the major amputation and death was studied by applying the Kaplan Meier approach and product/limit curves were built up.

The Stata 7.0 software package (Statistics/Data Analysis, Stata Corporation, 4905 Lakeway Drive, College Station, Texas 77845 USA, 800-STATA-PC) was used.

Results

Patient population and treatment

From January 1, 1999 to December 31, 2003, 902 diabetic patients were consecutively hospitalized for foot ulcer and/or rest pain.

567 patients in whom our diagnostic protocol indicated the presence of CLI were referred to an angiographic study. Three patients had no angiographic evidence of stenoses > 50% of vessel diameter, and were excluded from the analysis. Thus the study population included 564 (62.5%) patients.

Revascularization was performed in 537 (95.2%) patients.

PTA was performed in 420 (74.5%) patients. Table 1 reports the number of treated stenoses and occlusions, the number of stents placed in every artery of the ischemic limb and the rate of successful PTA procedures.

A BPG was performed in 117 (20.7%) patients. The BPG was axillo-femoral in one patient, femoral-popliteal (16 PTFE, 45 vein graft) in 61 patients, femoral-infrapopliteal (17 PTFE, 40 vein graft) in 57 patients. In 22 of these 117 patients a combined procedure, PTA plus BPG, was performed: in 10 patients an iliac PTA and femoral-popliteal BPG, in 12 patients femoral-popliteal BPG and an infrapopliteal PTA.

In 27 (4.8%) patients neither a PTA nor a BPG was possible due to high surgical risk or lack of outflow. In all these patients a treatment with prostanoids was started, but was immediately stopped in 5 patients for hypotension and in 2 for angina. In 5 patients a percutaneous chemical sympathectomy was also performed, while in the remaining patients this procedure was not considered appropriate due to the presence of a serious cardiopathy and other comorbidities (Table 2).

The ankle-pressure could not be measured in 297 (52.7%) patients, because of the absence of both tibial arteries in 105 patients or due to the presence of arterial calcifications in 192 patients.

PTA and BPG complications

Table 3 reports the non fatal complications in PTA and BPG patients.

In-hospital mortality

Four patients died during their hospital stay. Three BPG patients died: 1 for pneumonia, 1 for acute myocardial infarction and 1 for congestive heart failure. One non-revascularized patient died suddenly the night following the angiographic study.

Early limb salvage

Of the 537 revascularized patients, in 85 patients with rest pain without foot ulcer the pain disappeared and the antalgic medication was discontinued. In 443 patients with foot ulcers a complete healing of the lesions occurred with dressing or minor amputation. Nine (1.7%) major amputations were carried out at 30 days. Two above- and 4 below-the-knee amputations (1.4%) were performed in PTA patients, in 5 for extensive infection of surgical wound of a Chopart amputation, and in 1 for acute distal thrombosis after PTA not suitable for surgical revascularization. Of these six major amputations, three were performed in patients treated without stent and three in patients treated with stent, without significant difference ($p = 0.358$). Three (2.6%) above-the-knee amputations were performed in BPG patients with crural by-pass, 2 with PTFE and 1 with venous conduit following acute non treatable graft closure.

Of the 27 non-revascularized patients, in 2 patients the foot lesion healed with dressing whereas in 14 patients major amputation (10 above- and 4 below-the-knee) was performed at 30 days for rest pain and extensive gangrene. In the other 11 patients the foot lesion did not heal but there was not worsening, the pain decreased but did not disappear and the antalgic medication was reduced but not discontinued.

Follow-up

558 (98.9%) patients, 415 of the PTA group, 116 of the BPG group and 27 of non revascularized group, were

Table 1. Number of treated stenoses and occlusions, their percent of TASC non eligible, number of stents placed in every artery and percent of success of PTA procedures

Artery	Stenoses	Length > 4 cm	Successful pta	Stents	Occlusions	Length > 2 cm	Successful pta	Stents
Iliac trunk	31	10 (32.3%)	31 (100%)	19	4	2 (50.0%)	4 (100%)	4
Femoral	146	97 (66:4)	146 (100%)	8	78	51 (65.4%)	78 (100%)	40
Popliteal	112	41 (36.6%)	112 (100%)	1	36	16 (44.4%)	36 (100%)	18
Anterior tibial	91	80 (87.9%)	76 (83.5%)	–	257	232 (90.3%)	63 (24.5%)	6
Posterior tibial	57	45 (78.9%)	46 (80.7%)	–	291	262 (90.0%)	40 (13.7%)	7
Peroneal	125	89 (71.2%)	100 (80.0%)	–	124	77 (62.1%)	32 (25.8%)	4

A concomitant femoral-popliteal and crural PTA was performed in 151 patients: in 116 with angioplasty of one crural artery, more than one in 35 patients.

Table 2. Demographic and clinical characteristics of study population (N = 564) in revascularized patients with PTA and BPG, and in revascularized and non revascularized patients

Variables	PTA n = 420	BPG n = 117	*p*	Revascularized patients n = 537	Non revascularized patients n = 27	*p*
Age (years)	69.7 ± 9.4	69.8 ± 9.6	0.910	69.8 ± 9.5	76.7 ± 10.4	0.001
Females (n)	148 (35.2%)	37 (31.6%)	0.467	185 (34.9%)	13 (48.1%)	0.146
Insulin therapy (n)	255 (60.7%)	73 (62.4%)	0.742	328 (61.1%)	14 (51.9%)	0.338
Diabetes duration (years)	17.7 ± 11.4	14.9 ± 9.9	0.020	17.1 ± 11.1	13.4 ± 10.0	0.013
Sensory-motor neuropathy (n)	343 (81.7%)	98 (83.8%)	0.600	441 (82.1%)	24 (88.9%)	0.367
Creatinine (mg/dl) (n = 532)	1.29 ± 0.5	1.25 ± 0.4	0.470	1.28 ± 0.5	1.15 ± 0.36	0.208
Dialysis (n)	24 (5.7%)	8 (7.0%)	0.650	32 (5.9%)	–	–
Antihypertensive therapy (n)	304 (72.4%)	72 (61.5%)	0.240	376 (70.0%)	20 (74.1%)	0.653
Cardiac disease (n)	225 (53.6%)	64 (54.7%)	0.566	289 (53.8%)	24 (88.9%)	0.003
Ejection fraction (%, n = 323)	49.1 ± 10.8	49.6 ± 10.1	0.700	49.2 ± 10.5	38.34 ± 8.4	0.001
History of stroke (n)	55 (13.1%)	19 (16.2%)	0.380	74 (13.8%)	9 (33.3%)	0.005
Wagner grade (n) 0	66 (15.7%)	19 (16.2%)	0.822	85 (15.8%)	3 (11.1%)	0.840
1	64 (15.2%)	14 (12.0%)		78 (14.5%)	5 (18.5%)	
2	59 (14.0%)	14 (12.0%)		73 (13.6%)	5 (18.5%)	
3	41 (9.8%)	11 (9.4%)		52 (9.7%)	3 (11.1%)	
4	190 (45.2%)	59 (50.4%)		249 (46.4%)	11 (40.7%)	
Infected ulcer (n)	270 (64.3%)	75 (64.1%)	0.971	345 (64.2%)	17 (63.0%)	0.892
TcPO2 before the treatment (mmHg)	15.3 ± 11.9	10.3 ± 10.6	0.001	13.8 ± 11.2	7.0 ± 8.1	0.001
TcPO2 after the treatment (mmHg)	44.9 ± 12.1	38.9 ± 12.0	0.690	41.6 ± 12.1	11.4 ± 8.6	0.001

followed from January 1st 1999 until June 30th 2005. The mean follow-up was 3.4 ± 1.3 years.

CLI recurrence during follow-up

A first episode of clinical restenosis in the PTA group occurred in 76 (18.3%) patients. The cumulative patency rate at 5 years was 78% (CI 71–83%). PTA procedures were successfully repeated in 62 (81.6%) patients and 1 patient died suddenly the night after PTA. In the remaining 14 patients a further PTA was not feasible, and 8 patients underwent a BPG.

Non-treatable graft closure occurred in 22 (18.8%) patients of the BPG group. The cumulative patency rate at 5 years was 77% (CI 67–85%).

Table 3. Non fatal complications and their treatment in revascularized patients (N = 537)

PTA patients (N = 420)	**N**	**Treatment**
Myocardial infarction	1	Intensive care unit
Angina	1	Medical treatment
Cardiac arrhythmia	1	Intensive care unit
Left ventricular failure	1	Medical treatment
Chest pain	1	Investigation, no treatment
Acute renal failure	1	Medical treatment without dialysis
Haematoma at the access site	2	Transfusion
	1	Investigation without therapy
Access site pseudoaneurysms	3	Surgical treatment
Thrombosis	5	Thrombolysis effectiveness
	1	Above-the-knee amputation
BPG patients (N = 117)	**N**	**Treatment**
Thrombosis	8	Thrombectomy
	3	Above the knee amputation
Venous fistula	1	Surgical ligature

Major amputation during follow-up

Thirty-two major amputations were performed. Three above- and 13 below- the-knee amputations were performed in the PTA group, 14 because of recurrence of rest pain and extensive gangrene due to non-treatable restenosis and 2 because of osteomyelitis of the heel. Ten above- and 4 below-the-knee amputations were performed in the BPG group because of non-treatable occlusion of the graft and 1 patient died during hospital stay because of septic shock. Among the major amputations in BPG group, 3 were performed in patients with femoral-popliteal graft (2 PTFE, 1 venous conduit), and 11 in infrapopliteal graft (8 PTFE, 3 venous conduit). Two above-the-knee amputations were performed in non revascularized patients because of a foot lesion worsening.

Table 4 summarize the number of major amputations performed in the early and follow-up period. Fig. 1 shows the Kaplan-Meier curves of major amputation in the three groups. The results of multiple logistic regression analysis performed for the association between the recorded variables and the above-the-ankle amputation are showed in Table 5.

173 (30.7%) patients died during follow-up. 120 (28.9%) patients died in the PTA group, 31 (26.7%) in the BPG group and 22 (81.4%)in the non-revascularized group. Fig. 2 shows the Kaplan-Meier survival curves of the three groups. The causes of death are reported in Table 6. Table 7 reports the Hazard Ratio of the Cox model performed for the association between the recorded variables and mortality.

Table 4. Number of above-the-ankle amputations performed in the early and follow-up period in PTA, BPG and no revascularized patients

Patients treatment	Above-the-ankle amputation		Total
	At 30 days	Follow-up	
Angioplasty (N = 420)	6 (1.4%)	16 (3.8%)	22 (5.2%)
Bypass graft (N = 117)	3 (2.6%)	14 (12%)	17 (14.5%)
No revascularization (N = 27)	14 (51.9%)	2 (7.4%)	16 (59.3%)

Table 5. Multiple logistic regression analysis between recorded variables and above-the-ankle amputation

Variables	Odds ratio	*p*	Confidence interval
Absence of revascularization (n)	35.9	<0.001	12.9–99.7
Occlusion of each of the crural arteries (n)	8.20	0.022	1.35–49.6
Wound infection (n)	2.1	0.004	1.3–3.6
Dialysis (n)	4.7	0.001	1.9–11.7
$TcPO_2$ increase (1 mmHg)	0.80	<0.001	0.74–0.87

Discussion

In this study patients were enrolled consecutively. No diabetic patient with TASC parameters of CLI were excluded. The percentage of patients undergoing revascularization was very high considering that PTA and BPG were performed in a population enrolled consecutively and not in selected patients with a presumed high success of revascularization.[12]

The high revascularization rate of our cases depends on the use of both PTA and BPG. Many patients who underwent PTA were not suitable for BPG because their three leg arteries or pedal arteries were not patent or because of the high surgical risk. A high percentage of patients in whom PTA was not feasible were revascularized with BPG. In our protocol PTA was the first-choice procedure of revascularization allowing outcomes similar to BPG.[13] In our practice PTA is effective also in long obstructions of the infrapopliteal arteries.[14,15] The in-hospital mortality was very low in PTA patients, and was also low in BPG patients in comparison with the literature data.[16]

Revascularization is the best therapy to eliminate pain and heal foot lesion in patients with CLI.[17,18] Revascularization is especially necessary when a foot surgery is required.[19,20] The extensive use of revascularization, in association with a good surgical approach to the foot lesion, resulted in the short period in a very high rate of limb salvage.[2,21,22]

However, major amputation were noted during follow-up. In the PTA group most of the major amputations were performed for clinical restenosis without further possibility of endoluminal or surgical revascularisation. All the major amputations of BPG group were performed because of graft closure. Although some studies reported a higher rate of pedal by-pass failure in the early period than in the follow-up,[23,24] our data seem to be consistent with the fast progression of atherosclerosis and the predominantly crural localization of the atherosclerotic obstructions, which are typical features in diabetic patients.[25,26]

The major amputation rate of the non-revascularized patients is very different. The early major amputation rate of these patients is very high. The low percentage during the follow-up can be explained by the very low survival rate of these patients due the associated serious comorbid conditions, cardiac especially. The

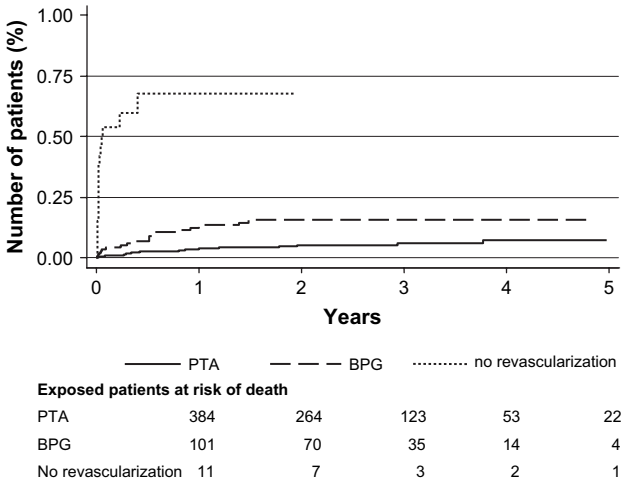

Fig. 1. Kaplan-Meier above-the-ankle amputation estimates in PTA, BPG and non revascularized patients.

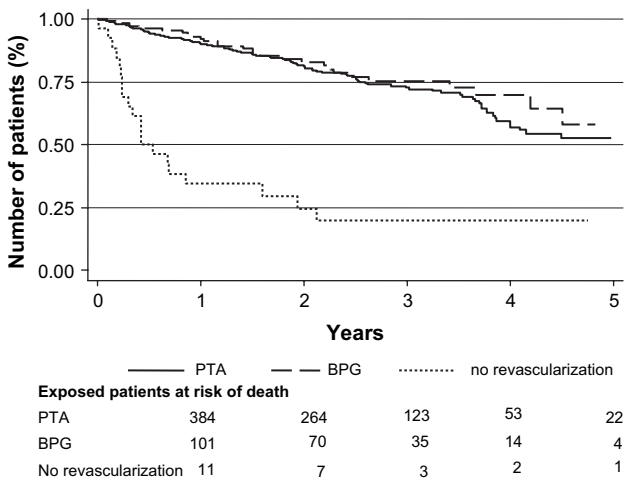

Fig. 2. Kaplan-Meier survival estimates of PTA, BPG and non revascularized patients.

Table 6. Causes of death in followed population (N = 558)

Cause of death	PTA N = 415	BPG N = 116	No revascularization N = 27
Cardiac disease	64	15	14
Sudden death	12	4	1
Stroke	18	3	4
Cancer	12	5	2
Pulmonary embolism	–	1	–
Abdominal aneurysm	1	–	–
Renal insufficiency	4	–	–
Peritonitis	1	–	–
Gastric hemorrhage	1	–	–
Cirrhosis	2	–	–
Pneumonia	2	2	–
Geromarasmus	2	–	1
Septic shock	–	1	–
Suicide	1	–	–
Total	120 (28.9%)	31 (26.7%)	22 (81.5%)

mortality rate is high also in revascularized patients, although it is lower than in the non-revascularized patients.[27–30]

In order to achieve the best health-related quality of life we aim to avoid major amputation in all patients, except in patients unable to walk and mentally incapable.

In conclusion revascularization with PTA or BPG allows a very high percentage of limb salvage in diabetic patients with CLI. In the early period the revascularization, in association with a good medical and surgical approach to foot lesion, results in a very high percentage of limb salvage, with very low in hospital mortality rate. During the follow-up the risk of above-the-ankle amputation is higher, but still lower compared to the literature data in non-revascularized patients with CLI.[31,32] Impossibility of revascularization because of the extent of arterial occlusive disease or surgical risk is a reliable marker both of a very high risk of major amputation and of a very low life expectancy, because of the severity of the comorbid conditions associated with the severity of CLI.

Table 7. Cox model for association between recorded variables and mortality

Variables	Hazard ratio	*p*	Confidence interval
Age (1 year)	1.05	<0.001	1.03–1.07
History of cardiac disease (n)	2.16	<0.001	1.53–3.06
Dialysis (n)	3.52	<0.001	2.08–5.97
Absence of revascularization (n)	1.68	<0.001	1.29–2.19
Impaired ejection fraction (1%)	1.08	<0.001	1.05–1.09

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